Claims

We claim:

1. An immunogenic composition comprising a capsular polysaccharide or oligosaccharide of *Haemophilus influenzae* B (PRP), and a polyanionic polymer.

2. The immunogenic composition of claim 1, wherein PRP is conjugated to a carrier protein which is a source of T-helper cell epitopes.

3. The immunogenic composition of claim 2, wherein the carrier protein is selected from the group consisting of: tetanus toxoid, diphtheria toxoid, CRM197, and protein D.

4. The immunogenic composition of claims 1-3, the polyanionic polymer having anionic constitutional repeating units.

5. The immunogenic composition of claims 1-4, wherein the polyanionic polymer comprises anionic constitutional repeating units obtained from a group consisting of: acrylic acid, methacrylic acid, maleic acid, fumaric acid, ethylsulphonic acid, vinylsulphuric acid, vinylsulphonic acid, styrenesulphonic acid, vinylphenylsulphuric acid, 2-methacryloyloxyethane sulphonic acid, 3- methacryloyloxy-2-hydroxypropanesulphonic acid, 3-methacryl amido-3- methylbutanoic acid, acrylamidomethylpropanesulfonic acid, vinylphosphoric acid, 4-vinylbenzoic acid, 3-vinyl oxypropane-1-sulphonic acid, N-vinylsuccinimidic acid, and salts of the foregoing.

6. The immunogenic composition of claims 1-4, wherein the polyanionic polymer is an oligo- or poly-saccharide such as dextran.

7. The immunogenic composition of claims 1-4, wherein the polyanionic polymer is an oligo- or poly-peptide and comprises anionic constitutional repeating units obtained

from a group consisting of: L-aspartic acid, D-aspartic acid, L-glutamic acid, D-glutamic acid, and salts of the foregoing.

8. The immunogenic composition of claim 7, wherein the polyanionic polymer is an oligo- or poly-peptide which has a monomer content of no less than 30, 40, 50, 60, 70, 80, 90 or 100% L-aspartic acid and/or L-glutamic acid.

9. The immunogenic composition of claim 7 or 8, wherein the oligo- or polypeptide consists of, on average, 4-200 or 5-200 residues, preferably 8-117 residues, more preferably 15-18 residues, most preferably 17 residues.

10. The immunogenic composition of claims 1-9, wherein the polyanionic polymer is polyanionic heteropolymer.

11. The immunogenic composition of claim 10, wherein the polyanionic heteropolymer consists of two distinct anionic constitutional repeating units.

12. The immunogenic composition of claims 1-9, wherein the polyanionic polymer is a polyanionic homopolymer.

13. The immunogenic composition of claim 12, wherein the polyanionic polymer is poly-L-glutamic acid (PLG).

14. The immunogenic composition of claims 1-13, wherein the result of multiplying the concentration of the polyanionic polymer (in μM) by the net negative charge of the polyanionic polymer at pH 7.0 divided by the amount of PRP present in a 0.5 mL dose of the immunogenic composition (in μg) is 300-6000, preferably 400-4000, more preferably 500-2000, 560-1100, 610-900, 640-800, or 660-700, and most preferably around or exactly 680.

15. The immunogenic composition of claims 1-14, wherein the concentration of the polyanionic polymer in the composition is 30-2000 in μM.

16. The immunogenic composition of claims 1-15, wherein the polyanionic polymer has a net negative charge at pH 7.0, on average, of at least 8, and preferably at least 17.

17. The immunogenic composition of claims 1-16, wherein the polyanionic polymer has at least on average 1 net negative charge at pH 7.0 per 3 monomers, preferably at least 2 per 3 monomers, and most preferably at least on average 1 net negative charge for each monomer.

18. The immunogenic composition of claims 1-17, wherein the amount of PRP present in a 0.5 mL dose of the immunogenic composition is 1-20, preferably 2.5-10, and most preferably around or exactly 5 μg.

19. The immunogenic composition of claims 1-18, wherein the immunogenic composition comprises one or more further antigens.

20. The immunogenic composition of claim 19, wherein the one or more further antigens comprise one or more meningococcal capsular oligosaccharide or polysaccharide – carrier protein conjugates selected from a group consisting of: MenC, MenY, MenA and MenW, preferably MenC and/or MenY.

21. The immunogenic composition of claim 19 or 20, wherein the one or more further antigens comprise one or more pneumococcal capsular oligosaccharide or polysaccharide – carrier protein conjugates.

22. The immunogenic composition of claim 20 or 21, wherein the carrier protein is selected from the group consisting of: tetanus toxoid, diphtheria toxoid, CRM197, and protein D.

23. The immunogenic composition of claims 19-22, wherein the one or more further antigens comprise tetanus toxoid, diphtheria toxoid, and inactivated whole-cell *B. pertussis* or one or more acellular *B. pertussis* antigens.

24. The immunogenic composition of claims 19-23, wherein the one or more further antigens comprise one or more acellular *B. pertussis* antigens selected from the group consisting of: pertussis toxiod, FHA, pertactin, agglutinogen 2 and agglutinogen 3.

25. The immunogenic composition of claims 19-24, wherein the one or more further antigens comprise either or both of Inactivated Polio Vaccine (IPV) and Hepatitis B surface antigen, wherein Hepatitis B surface antigen is preferably adsorbed onto aluminium phosphate.

26. The immunogenic composition of claims 19-25, which further comprises an adjuvant with a zero point charge greater than 8; wherein the polyanionic polymer prevents flocculation between the adjuvant and PRP and/or reduces the immunological interference that the adjuvant has on PRP.

27. The immunogenic composition of claim 26, wherein the adjuvant is selected from the group consisting of: alum and aluminium hydroxide.

28. The immunogenic composition of claim 26 or 27, wherein the adjuvant is present in the immunogenic composition in the amount of 100-1000 μg per 0.5 mL dose.

29. The immunogenic composition of claims 26-28, wherein at least one of the one or more further antigens is adsorbed onto the adjuvant.

30. The immunogenic composition of claim 29, wherein the presence of the polyanionic polymer does not cause significant desorption of the one or more further antigens adsorbed onto the adjuvant.

31. The immunogenic composition of claim 29 or 30, comprising the following antigens adsorbed onto aluminium hydroxide: diphtheria toxoid, tetanus toxoid, pertussis toxoid, FHA and pertactin.

32. The immunogenic composition of claim 31, further comprising unadsorbed IPV and/or Hepatitis B surface antigen adsorbed onto aluminium phosphate.

33. The immunogenic composition of claims 1-32, which is lyophilised and further comprises a stabilizing excipient selected from the group consisting of: glucose, maltulose, iso-maltulose, lactulose, sucrose, sorbitol, maltose, lactose, iso-maltose, maltitol, lactitol, palatinit, trehalose, raffinose, stachyose, and melezitose; preferably sucrose.

34. A vaccine comprising the immunogenic composition of claims 1-33 and a pharmaceutically acceptable excipient.

35. A method of preventing or treating *H. influenzae* B disease comprising the steps of administering a pharmaceutically effective amount of the vaccine of claim 34 to a patient in need thereof.

36. The use of the immunogenic composition of claims 1-33 or the vaccine of claim 34 in the manufacture of a medicament for the prevention or treatment of *H. influenzae* B disease.

37. A method to reduce the immunological interference of a *Haemophilus influenzae* B capsular polysaccharide or oligosaccharide (PRP), preferably conjugated, in a combination vaccine comprising one or more further antigens adsorbed to an adjuvant with a zero point charge greater than 8, wherein such method comprises the steps of:

(i) adsorbing the one or more further antigens onto the adjuvant;

(ii) adding a polyanionic polymer to said one or more further antigens; and

(iii) then adding an immunogenic composition comprising PRP to said one or more further antigens.

38. The method of claim 37, wherein the combination vaccine is the immunogenic composition of any one of claims 26-32.

39. A method to reduce the immunological interference of a *Haemophilus influenzae* B capsular polysaccharide or oligosaccharide (PRP), preferably conjugated, in a combination vaccine comprising one or more further antigens adsorbed to an adjuvant with a zero point charge greater than 8, wherein such method comprises the steps of:

(i) adsorbing the one or more further antigens onto the adjuvant; and

(ii) adding an immunogenic composition comprising PRP and a polyanionic polymer to said one or more further antigens.

40. The method of claim 39, wherein the immunogenic composition is that of any one of claims 1-18.

41. The method of claim 39 or 40, wherein the combination vaccine is the immunogenic composition of any one of claims 26-32.

42. The method of any one of claims 37-41 wherein the immunogenic composition is added extemporaneously to said one or more further antigens.

43. The method of claims 37-39, wherein the immunogenic composition is lyophilised in the presence of a stabilizing excipient selected from the group consisting of: glucose, maltulose, iso-maltulose, lactulose, sucrose, sorbitol, maltose, lactose, iso-maltose, maltitol, lactitol, palatinit, trehalose, raffinose, stachyose, and melezitose; preferably sucrose.

44. The method of claims 37-43, wherein the immunogenic composition further comprises one or more conjugated meningococcal capsular oligosaccharides or

polysaccharides selected from a group consisting of: MenC, MenY, MenA and MenW, preferably MenC and/or MenY.

45. The method of claims 37-44, wherein the immunogenic composition further comprises one or more conjugated pneumococcal capsular oligosaccharides or polysaccharides.

46. The method of claims 37-45, wherein the adjuvant is aluminium hydroxide.

47. The method of claims 37-44, wherein the one or more further antigens comprise the following antigens: diphtheria toxoid, tetanus toxoid, pertussis toxoid, FHA and pertactin.

48. The method of claims 37-45, wherein the presence of the polyanionic polymer in the combination vaccine does not cause significant desorption of the one or more further antigens adsorbed to the adjuvant.

49. The use of a polyanionic polymer in an immunogenic composition further comprising a *Haemophilus influenzae* B capsular polysaccharide or oligosaccharide (PRP), preferably conjugated, as a means for protecting the immune response of PRP.

50. The use of claim 49, wherein the immunogenic composition is that of claims 1-33.

51. A kit comprising: i) a first immunogenic composition comprising a *Haemophilus influenzae* B capsular polysaccharide or oligosaccharide (PRP), preferably conjugated, and a polyanionic polymer; and ii) a second immunogenic composition comprising one or more antigens adsorbed onto an adjuvant with a zero point charge greater than 8.

52. The kit of claim 51, wherein the first immunogenic composition is the immunogenic composition of claims 1-25.

53. The kit of claim 51 or 52, wherein the first immunogenic composition is lyophilised and further comprises a stabilizing excipient, preferably sucrose, and the second immunogenic composition is liquid.

54. The kit of claims 51-53, wherein the first immunogenic composition further comprises one or more conjugated meningococcal capsular oligosaccharides or polysaccharides selected from a group consisting of: MenC, MenY, MenA and MenW, preferably MenC and/or MenY.

55. The kit of claims 51-54, wherein the first immunogenic composition further comprises one or more conjugated pneumococcal capsular oligosaccharides or polysaccharides.

56. The kit of claims 51-55, wherein the adjuvant is aluminium hydroxide.

57. The kit of claims 51-56, wherein the second immunogenic composition comprises one or more antigens selected from a group consisting of: diphtheria toxoid, tetanus toxoid, pertussis toxoid, FHA and pertactin.

58. The use of a polyanionic polymer in the manufacture of an immunogenic composition for the prevention of aggregation or flocculation occurring in said composition.

59. An immunogenic composition comprising a saccharide antigen with a pI less than 3, and a polyanionic polymer.